REMARKS

As a preliminary matter, it is noted that no claims have been currently amended.

As a further preliminary matter, it is assumed that reference to claims 72-148 being subject to a restriction and/or election requirement (item 8 on the summary sheet) was a typographical error since no restriction was in fact imposed in the current office action.

Claims 72-76, 80-86, 93-129, 133-139, and 146-148 are currently in the application and stand rejected, as explained in detail below. Claims 77-79, 87-92, 130-132, and 140-145 were previously withdrawn as being directed to a non-elected species.

Claims 72-76, 80-86, 93-129, 133-139, and 146-148 were rejected over Handsfield in view of Urquhart (US 4,851,231), and Edgren (US 4,522,625) in further view of Etienne (US 4,755,385) and Periti. Handsfield, Urquhart, and Edgren were cited for the same reasons advanced in previous office actions. Etienne and Periti were newly cited. The Examiner stated, in pertinent part:, that

> Claims 72-76, 80-86, 93-129, 133-139, and 146-148 are rejected under 35 USC 103(a) as being unpatentable over Handsfield et al. in view of Urquhart (US Pat. 4,851,231), Edgren (US Pat. 4,522,625) for the reasons of record set forth in the prior Office Actions in further view of Etienne et al. (US Pat. 4,755,385) and Periti et al. (Abstract) and the further reasons below.
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> Hansfield, Urquhart and Edgren are cited for the same reasons as the prior Office Action and the same are incorporated herein.
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> Etienne et al. disclose many macrolide antibiotics, such as erythromycin and AS-E 136 are sensitive to acidic media and are usually destroyed by the action of gastric juices (Column 1, lines 34-38). It is disclosed that it is well known to compress active substances with suitable excipients to form a tablet and coat a tablet with gastric juice-resistant lacquers such as cellulose acetate phthalate or hydroxyl-propylmethylcellulose phthalate which after leaving the stomach the lacquer dissolves in the intestinal juices and the active substance is dissolved and resorbed (Column 2, lines 25-53). It is disclosed that resistant to gastric juices means that the preparation should release virtually no active substance for a period between 30 minutes and 2 hours and having a pH solubility of between 5.5 and 6.8 or which releases the active substance at a pH of between 5.5 and 6.8, preferably, between 6.0 and 6.4 (Column 4, lines 5-10, 60-68, Column 5, lines 1-6). Tests are performed using USPXX apparatus at 100 rpm at pHs of 1.2, 4.5, 6.0, 6.2, 6.4 and 6.5 (Examples 1-8).
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> Periti et al. discloses that azithromycin is acid unstable (although exhibiting increased acid stability over older macrolide antibiotics) (Abstract).
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> Examiner has duly considered Applicant's arguments but deems them moot in light of the new grounds of rejection herein.
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> Curatolo is no longer part of the rejection herein. Although erythromycin and azithromycin do have their differences, both erythromycin and azithromycin exhibit adverse gastric effects and are acid unstable (although azithromycin does

have increased acid stability over erythromycin). As such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to control the release of azithromycin to be released at least 30 minutes after ingestion so as to avoid adverse gastric effects and any acid instability by using an enteric coating which dissolves preferably at a pH of between 6.0 and 6.4. As such, one or ordinary skill in the art would expect that for enteric coatings which dissolve at pHs of greater than 6.0 that substantially no active agent will be released until the pH of the surrounding media, whether in vitro or in vivo, is at the appropriate pH. As such, such a dosage form will meet the criteria set forth in the claims.

Applicants' Traversal

As a preliminary matter, a brief review of the invention itself would be useful in laying some groundwork for Applicants' comments.

The invention relates to controlled release dosage forms of azithromycin, which dosage forms have an improved side effect profile. The scientific determination that underlies the invention is disclosed in the specification at page 6, lines 14-28:

> The inventors conducted a series of studies in man in which the incidence and severity of gastrointestinal side effects were assessed after dosing azithromycin intravenously, orally, duodenally (via nasoenteric intubation), and ileally (via nasoenteric intubation). The studies demonstrated that the incidence of gastrointestinal side effects is relatively low after intravenous dosing, even at doses which are equivalent to a 5.4 g oral dose. Thus, while not wishing to be limited by or to any particular theory or mechanism, the gastrointestinal side effects of orally dosed azithromycin appear to be mediated by local interactions between azithromycin and the intestinal wall. Furthermore, the nasoenteric intubation studies demonstrated that duodenal azithromycin dosing results in more severe gastrointestinal side effects than does ileal dosing. The inventors accordingly determined that dosing azithromycin in a manner which reduces exposure of the duodenum to high concentrations of the drug results in decreased gastrointestinal side effects.

As explained above, the inventors based the invention on their determination that azithromycin side effects are mediated locally, in the upper gastrointestinal (GI) tract, particularly the duodenum. It was the inventors who discovered the sensitivity of the duodenum to azithromycin. Applicants' Example 2 demonstrated that the duodenum was highly locally sensitive to azithromycin. That aspect was not previously known, nor is it disclosed in any of the references. It was this discovery that formed the basis by which the inventors solved the problem of azithromycin side effects by formulating

azithromycin in a controlled release dosage form that either reduces exposure of the upper GI tract to azithromycin or avoids such exposure altogether.

Prior to the inventors' clinical studies, there was no reason to formulate azithromycin in a controlled release dosage form because, among other reasons, of its long half-life. That is, azithromycin has a long half-life of 69 hours, meaning it takes 69 hours to purge half of the azithromycin administered in a previous dose. 69 hours is a very long time relative to the 6 hour time scale of claim 72 or the one-half hour time scale of claim 96. Thus, in relation to the patentability of the instant invention, there is a fundamental issue for consideration: - - what reason or motivation was there for one of ordinary skill in the art to formulate azithromycin in a dosage form that operates on a scale of several hours when azithromycin persists in the body for much, much longer, (one half still being present after a time on the order of 70 hours), in the first place? Only Applicants, by reason of the study they disclose in their specification (and as quoted above) had motivation to formulate azithromycin in a controlled release dosage form.

It is Applicants' position that the Examiner has failed to establish a prima facie case of obviousness. To establish a *prima facie* case, the Examiner must satisfy three requirements: (1) there must be some suggestion or motivation in the reference or in the knowledge generally available to one of ordinary skill in the art to modify the reference or combine reference teachings; (2) the proposed modification of the prior art must have had a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the limitations of the claims. MPEP § 2142. It is Applicants position that all three requirements are missing.

As to the first requirement (a suggestion or motivation grounded in the art itself), the fact that azithromycin is known as having some acid sensitivity in the stomach does not in and of itself supply motivation for incorporating azithromycin into a controlled release dosage form. Indeed, at the time of Applicants' earliest filing date (May, 1994) azithromycin was already on the market (US, Europe, and other countries) in a number of non-controlled release dosage forms. Thus the minimal acid sensitivity of azithromycin was not an issue in formulating an immediate release oral dosage form of azithromycin and did not represent a problem to be solved.

As to the second requirement (I.e., an expectation of success), prior to Applicants' clinical studies as reviewed above, there was no reason to have an expectation of success because it was not known that azithromycin side-effects were locally mediated. None of the references suggests that putting azithromycin in a

controlled release dosage form would solve a problem, hence provides any basis for having an expectation of success.

As to the third requirement (i.e., that the prior art disclose all elements of the invention), it is respectfully submitted that the Examiner has simply located references that disclose controlled release plus references that disclose azithromycin and its antibiotic activity. But there is no suggestion, absent Applicants' own application, to combine those separate elements. The references show that controlled release dosage forms were known and that azithromycin was known, but there is no basis. grounded in the references themselves, to effect their combination in such a way as to make Applicants' invention obvious.

The Examiner appeared to be trying to supply the missing motivation for an obviousness rejection through the citation of Periti and Etienne, and referred to both references as supporting the contention that (1) macrolides in general are acid sensitive (Etienne), (2) including azithromycin (Periti). The Examiner summed up by stating:

> Although erythromycin and azithromycin do have their differences, both erythromycin and azithromycin exhibit adverse gastric effects and are acid unstable (although azithromycin does have increased acid stability over erythromycin). As such, it would have been well within the skill of and one of ordinary skill in the art would have been motivated to control the release of azithromycin to be released at least 30 minutes after ingestion so as to avoid adverse gastric effects and any acid instability by using an enteric coating which dissolves preferably at a pH of between 6.0 and 6.4.

Applicants traverse the rejection on the basis that it is based on hindsight. One of ordinary skill in the art would not find it obvious to make a sustained release dosage form of azithromycin absent a motivation or a benefit. But, and as discussed above, that motivation/benefit is simply not present in the references cited by the examiner because the minimal acid sensitivity of azithromycin was not a barrier to making it into a safe and effective immediate release dosage form. The following reasons apply.

First, the impetus for making the invention was, as stated above, the determination by the inventors that azithromycin side effects are mediated locally, in the upper gastrointestinal (GI) tract, especially the duodenum. Certainly neither of the newly-cited documents, Etienne and Periti, nor any of the references previously cited, discloses anything relating to the problem of upper-GI mediation of azithromycin side effects.

The Etienne patent in fact demonstrates the patentability of the claimed invention by showing that the formulation arts can in fact be unpredictable depending, for example, on the particular antibiotic being considered. Etienne, for example, disclosed that

> It would not be difficult, for example, to develop a reliable pharmaceutical form for an active substance such as erythromycin which is susceptible to gastric juices since the active substance is sufficiently stable in the upper section of the intestine (pH about 5 to 5.5). In this case, it is well known to compress the active substance to form a tablet, e.g. with suitable excipients and coat this tablet so-called gastric juice resistant laquers such as cellulose acetate phthalate or hydroxyl-proprylmethyl cellulose phthalate. After leaving the stomach this laquer dissolves in the intestinal juices, the active substance is dissolved and resorbed. [Column 2, lines 32-44]

However, Etienne also pointed out that the above solution would not work for AS-E 136, the erythromycin derivative that was the focus of his disclosure:

> This known principle cannot be applied to AS-E 136 since the active substance only acquires stability at a pH of 7.5, as shown in Table 3. However, this pH is not generally attained in the intestines ...[Column 2, lines 44-47]

Etienne thus underscores Applicants' previous argument that quick and/or easy conclusions can not be drawn from the fact that one antibiotic looks like or is structurally related to another. That is, Etienne provides additional support in addition to the Declaration Applicants submitted with their previous response. That Declaration (i.e., a copy of a Declaration submitted during the prosecution of US 6,068,859) unequivocally demonstrated that no quick and easy conclusions can be drawn about azithromycin from what is known about erythromycin. The two drugs are simply too dissimilar in their behavior and their properties to make any simple, automatic conclusions.

Handsfield, Urquhart, and Edgren, as discussed in previous responses, add nothing to Etienne and Periti, Applicants' response to previous rejections based on those references being incorporated by reference herein. Edgren is simply an example of a controlled release dosage form, but with no suggestion to control the release of azithromycin. Handsfield simply demonstrates that azithromycin is a good, effective antibiotic, but fails to mention anything about controlled release. Edgren, like Urquhart, simply discloses certain types of controlled release dosage forms but, contains no

disclosure that would lead one of only ordinary skill in the art to apply any consideration of controlled release to azithromycin.

Reconsideration and withdrawal of the §103(a) rejection is accordingly respectfully requested.

Claims 72-76, 80-86, 93-129, 133-139, 146-148 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-76 of US Patent No. 6,068,859 in view of Handsield, Etienne et al. (US Pat. 4,755,385) and Periti et al. (Abstract). The Examiner stated, in pertinent part:

> Claims 1-76 disclose a controlled release dosage form in which not more than certain amounts of azithromycin are released within a time period after ingestion. "Controlled release" is defined to not include dosage forms which release more then 70% of their contained azithromycin within one half hour or less (Column 2, lines 9-12).
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> Hansfield, Etienne et al (US Pat. 4,755,385) and Periti et al. (Abstract) are cited herein for the same reasons as above and are incorporated herein to avoid repetition.
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> The difference between the claims of the US Patent and the claimed invention is that the claims of the US Patent do not recite in vitro characteristics. However, the prior art amply suggests the same as the prior art discloses using USP criteria for determining release of active agents in various pH and the desirability of formulations which release at pHs greater than 6. As such, one of ordinary skill in the art would expect that formulation prepared under said criteria would exhibit in vitro characteristics the same or similar to that set forth in the claimed invention.
>
> Therefore, the claimed inventions, as a whole, would have been an obvious modification of the claims of US Pat. 6,068,859 to one of ordinary skill in the art at the time the invention was made, because very element of the invention has been collectively taught by the combined teachings of the references.

Although Applicants disagree with the rejection on the merits, Applicants traverse the rejection on the basis that it is illogical because no basis for it exists. The touchstone of double patenting is the timewise extension of the claims in a prior issuing reference patent (6,068,859 in this case) by a later issuing patent. Eli Lilly v. Barr Labs., Inc. 58 USPQ2d 1865, 1878 (Fed. Cir. 2001) ("The judicially-created doctrine of obviousness-type double patenting cements that legislative limitation [on the patentee's right to exclude] by prohibiting a party from obtaining an extension of the right to exclude through claims in a later patent that are not patentably distinct from claims in a commonly owned earlier patent.") The "later patent" here, of course, is the patent that will issue on the instant application. However, any patent issuing on the instant application will expire on April 13, 2015, i.e., 20 years from the earliest effective filing

date, namely the PCT filing date of April 13, 1995. That is to be compared with the nominal expiration date for the '859 application, May 30, 2017, i.e., 17 years from its May 30, 2000 date of issue, owing to the fact that it issued on a pre-GATT application (i.e., an application having a filing date prior to June 8, 1995). Thus any patent issuing on the instant application will nominally expire before '859. In different words, no timewise extension of the '859 patent can occur by reason of any patent issuing on the instant application because any such patent will expire first. Thus, double patenting cannot lie in the instant case, and it is accordingly respectfully requested that the double patenting rejection be withdrawn.

It is accordingly respectfully submitted that all of the above rejections should be withdrawn, and that no other issues remain outstanding in this application. In view of the foregoing comments and amendments, this case is believed to be in condition for allowance, and a Notice of Allowance is courteously solicited.

Respectfully submitted,

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